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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/613,588	07/03/2003	Tahir Nadeem Majid	USAV2003/0110 US NP	5546
5487	7590	01/06/2006	EXAMINER	
ROSS J. OEHLER AVENTIS PHARMACEUTICALS INC. ROUTE 202-206 MAIL CODE: D303A BRIDGEWATER, NJ 08807			DESAI, RITA J	
			ART UNIT	PAPER NUMBER
			1625	
DATE MAILED: 01/06/2006				

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	10/613,588	MAJID ET AL.	
	<b>Examiner</b>	<b>Art Unit</b>	
	Rita J. Desai	1625	

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 10/06/2005.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-3,5-16 and 18-24 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 3 is/are allowed.
- 6) ☒ Claim(s) 1,2,5-16 and 18-24 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |   |   |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                        | 4) <input checked="" type="checkbox"/> Interview Summary (PTO-413)          |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)    | Paper No(s)/Mail Date. <u>1/3/05</u> .                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date _____.  | 6) <input type="checkbox"/> Other: _____.                                   |

## **DETAILED ACTION**

### ***Continued Examination Under 37 CFR 1.114***

The request filed on 10/06/05 for a Continued Examination Application (RCE) under 37 CFR 1.114 based on parent Application No. 10/613,588 is acceptable and a RCE has been established. An action on the RCE follows.

Claims pending 1-3, 5-16, 18-24.

Claims 1-3, 11-13 are drawn to compounds and pharmaceutical composition.

Claim 5 is drawn to a complex composition.

Claims 6-10, 14-16, 18-24 are drawn to a method of treating.

In paper dated 2/05 the previous examiner had done a restriction and applicants had elected group I in that restriction.

The claims are again being further restricted by this examiner.

### ***Election/Restrictions***

Restriction to one of the following inventions is required under 35 U.S.C. 121:

- I-A. Claims 1-3, 11-13 in part drawn to compounds and pharmaceutical compositions of formula I, wherein D is an aryl, optionally substituted, a pyridyl or a thiophenyl all optionally substituted, A is an alkyl or a fluoroalkyl with its optional substitutions and B is a bond classified in class 546, 514, subclass 82, 293.

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I-B Claims 1-3, 11-13 in part , drawn to compounds and pharmaceutical compositions of formula I , wherein D is an alkyl, optionally substituted, A is an aryl optionally substituted and B is a bond , classified in class 546, 514 , subclass 82, 293.

I-C. Claims 1-3, 11-13 in part , drawn to compounds and pharmaceutical compositions of formula I , wherein D, A and B are in a different than in group I-A and I-B, classified in various classes and subclasses. A further election of a single disclosed species is required and this group may be subject to further restriction.

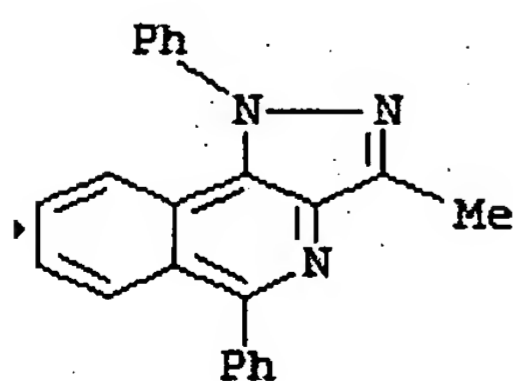
The inventions are distinct, each from the other because of the following reasons:

Inventions I-A, I-B and I-C are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions even though they have the pyrazolo isoquinoline common core , this core is not applicants contribution over the prior art. The novelty lies in the substitutions.

When a preliminary search was done on the core it gave numerous iterations.

Some of the compounds being as follows:-

1)



AN 1990:20931 CAPLUS

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DN 112:20931

TI Synthesis of 1,5-diaryl-3-methyl-1H-pyrazolo[4,5-c]isoquinolines and  
studies of binding to specific peripheral benzodiazepine binding sites

AU Cecchi, Lucia; Colotta, Vittoria; Melani, Fabrizio; Palazzino, Giovanna;  
Filacchioni, Guido; Martini, Claudia; Giannaccini, Gino; Lucacchini,  
Antonio

CS Dip. Sci. Farm., Univ. Firenze, Florence, 50121, Italy

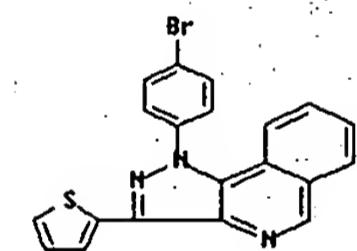
SO Journal of Pharmaceutical Sciences (1989), 78(6), 437-42

CODEN: JPMSAE; ISSN: 0022-3549

DT Journal

Reads on the compounds wherein A is an alkyl chain, R is a phenyl and B is a bond, D is a phenyl.

2)



in

AN 1999:392479 CAPLUS

DN 131:157733

TI Valence Bond Isomerization of Fused [1,2,3]Triazolium Salts with  
Bridgehead Nitrogen Atom. Fused Azolium Salts. 19

AU Beres, Mariann; Hajos, Gyoergy; Riedl, Zsuzsanna; Soos, Tibor; Timari,  
Geza; Messmer, Andras

CS Chemical Research Center Institute of Chemistry, Hungarian Academy of  
Sciences, Budapest, H-1525, Hung.

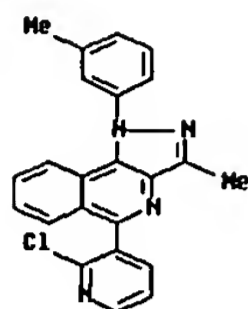
SO Journal of Organic Chemistry (1999), 64(15), 5499-5503

CODEN: JOCEAH; ISSN: 0022-3263

This reads on the compounds wherein A is a hetero aryl, B-D is a hydrogen and R is an aryl.

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3)



AN 1990:20931 CAPLUS

DN 112:20931

TI Synthesis of 1,5-diaryl-3-methyl-1H-pyrazolo[4,5-c]isoquinolines and  
studies of binding to specific peripheral benzodiazepine binding sites

AU Cecchi, Lucia; Colotta, Vittoria; Melani, Fabrizio; Palazzino, Giovanna;  
Filacchioni, Guido; Martini, Claudia; Giannaccini, Gino; Lucacchini,  
Antonio

CS Dip. Sci. Farm., Univ. Firenze, Florence, 50121, Italy

SO Journal of Pharmaceutical Sciences (1989), 78(6), 437-42

CODEN: JPMSAE; ISSN: 0022-3549

DT Journal

LA English

This reads on the compound when B is a bond A is an alkyl and R is an arylalkyl.

Thus with so many variables the **Search is burdensome to the PTO** and the groups I-A to I-C are **Independent and Distinct**.

Because these inventions are distinct for the reasons given above and the search required for Group I-A is not required for Group I-B or I-C, restriction for examination purposes as indicated is proper.

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During a telephone conversation with Mr. Gupta on 1/03/06 a provisional election was made with traverse to prosecute the invention of I-A, claims 1-3, 11-13 in part. Affirmation of this election must be made by applicant in replying to this Office action. Claims 5, 6-10, 14-16, 18-24 drawn to complex compositions and method of treating are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

If applicant's traverse on the grounds that the inventions are not patentably distinct, applicants should submit evidence or identify such evidence now of record showing the groups to be obvious variants or clearly admit on the record that this is the case. In either instance if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 USC 103 of the other invention.

Rejoinder:-

If applicants' compound claims are found to be allowable then the method of treating limited to the scope of the allowed claims will be rejoined provided there are no 112 issues.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

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The examiner has rejoined the method claims **Limited to the Scope** of the elected group IA.

***Claim Objections***

Claim 1 is unclear with R1 being defined in the middle. The proviso on page 6 is also not clear.

The COR1 and COOR1 is repeated.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claim 1-2, 11-13 are rejected under 35 U.S.C. 103(a) as being obvious over Flohr  
Stefanie et al US 6841556

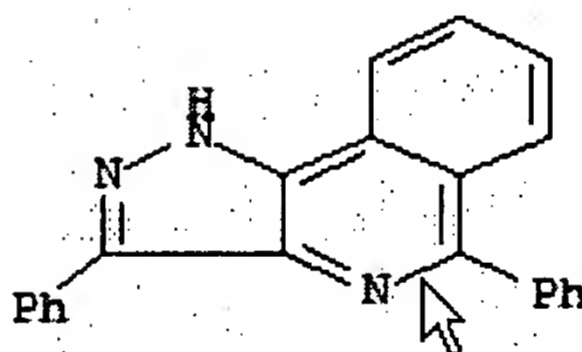
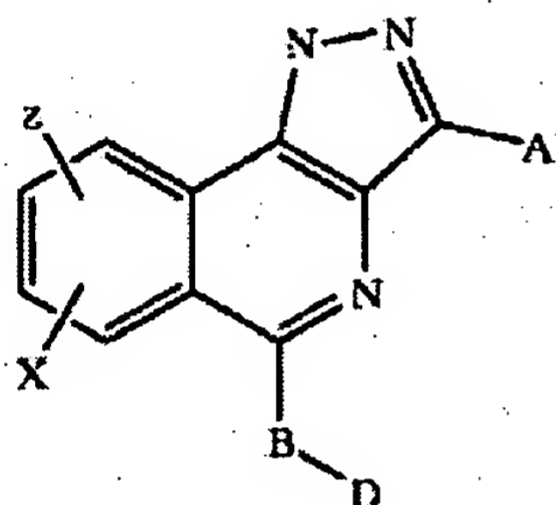
The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in

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the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Flohr Stefanie et al US 6841556

The reference discloses compounds of the formula



And the compounds disclosed are

These compounds read on the applicants compounds when R is an Hydrogen, A is an aryl and B is a covalent bond and D is a phenyl. These compounds are claimed generically.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

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pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5-10, 14-16, 18-24 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

To satisfy the Written description requirement, applicant must convey with reasonable clarity to one skilled in the art, as of the filing date that applicant were in possession of the claimed invention. Applicant's claims are drawn to compounds that can treat any disorder associated with an increased activity of NIK. The specification defines on pages 73-76 a few in vitro tests to test the TNF, cytotoxicity, IL6 activity, and others inhibitions. The specification gives no guidance to one of ordinary skill in the art that these any disorder can be treated.

*The expression "any disorder associated with an increased activity of NIK." does not convey to one of ordinary skill in the art that applicants were in possession of the claimed subject matter. The functional language recited without any correlation does not meet the written description requirement for the expression "any disorder associated with an increased activity of NIK. " as one of ordinary skill in the art could not recognize or understand which diseases /disorders are treated by the mere recitation of the function. Claims employing functional language at the point of novelty, such as applicants', neither provide those elements required to practice the inventions, nor "inform the public" during the life of the patent of the limits of the monopoly asserted. The expression could encompass myriad of diseases and*

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*applicants claimed expression represents only an invitation to experiment regarding possible treatments.*

**The level of predictability in the art:** It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427 F. 2d 833, 166 USPQ 18(CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. The level of unpredictability in the art is very high. The compounds which differ by a methyl group also show different properties, for e.g. theophylline and caffeine. One of them is a bronchodilator and they differ only by a methyl group.

**The state of the prior art:** There is very little known in the treatment of Alzheimer, , diabetes, stroke multiple sclerosis. The state of the prior art is that it involves screening in vitro and in vivo to determine which compounds exhibit the desired pharmacological activities. There is no absolute predictability and no established correlation between in vitro activity and the treatment of Alzheimer, , diabetes, stroke multiple sclerosis as the in vitro data is not a reliable predictor of success even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

**The amount of direction provided by the inventor:** The inventor provides very little direction in the instant specification. There are only 3 examples also there is no data provided to show that these compounds do indeed treat the various diseases as claimed. The only data provided is "that all the compounds have an IC<sub>50</sub> value." Even the Alzheimers test and the MS test on pages 75 and 76 just state that the compounds of the invention are generally expected to show

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improvement in clinical score. This is an invitation to experiment.

Considering the scope of the claim , unpredictability and guidance provided the specification lack a written description of what and how they would treat the various diseases.

Also compounds do not have an umbrella efficacy to be able to treat numerous diseases.

Claim 5 recites further containing other active agents also does not have a written description in the specifications. Page 20 line 10 just states other active ingredients without defining what they are.

Conclusion:-

The rejected of claims 1-3, 11-13 over Cecchi Lucia et al 1989 has been withdrawn.

Tully Wilfred GB 2185255 1987. have been withdrawn .

However claims 1,2, 5-16, 18-24 are rejected.

Claim 3 compounds are found to be allowable.

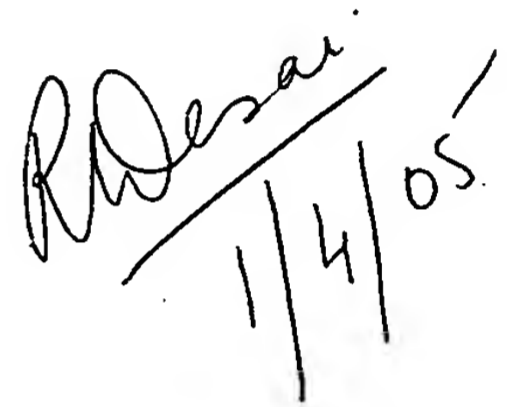
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rita J. Desai whose telephone number is 571-272-0684. The examiner can normally be reached on Monday - Friday, 9:30 am to 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Rita J. Desai  
Primary Examiner  
Art Unit 1625

Handwritten signature of Rita J. Desai and the date 1/4/05.

R.D.  
January 4, 2006